REMARKS

In response to the Office Action mailed June 8, 2009, Applicants have amended claims 1 and 10. No claims have been canceled and no new claims have been added. It is urged that support for all the above amendments may be found throughout the specification as originally filed, for example, on pages 24-26, and in Figs. 3 and 4. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made solely to clarify a particular aspect of the presently claimed invention, without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1-6 and 9-10 are pending and under examination. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

CLAIMS REJECTIONS UNDER 35 U.S.C. §112, ENABLEMENT, FIRST REJECTION

Claims 7, 8, and 10 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that treatment or prevention of HIV infection is not enabled because the metes and bounds of conditions which could not be treated or prevented cannot be ascertained.

Applicants respectfully submit that claims 7 and 8 were canceled in response to the Office Action dated December 19, 2008; thus, this basis of rejection is moot with regard to claims 7 and 8.

Applicants respectfully traverse this basis for rejection and submit that the as-filed specification fully enables the present claims. Moreover, one having ordinary skill in the art would be able to practice the entire breadth of the presently claimed invention without undue experimentation. Nevertheless, Applicants, without acquiescence, have amended claim 10 to recite:

> "A method for ~~the prevention and/or~~ treatment of HIV infection in a patient, comprising administrating the compounds according to any one of claims 1-3 ~~and the extract according to claim 4~~, wherein the compounds blocks the binding and

fusion between HIV and HIV uninfected CD4 cells, thereby ~~preventing and/or~~ treating HIV infection in the patient."

Support for this amendment can be found throughout the as-filed specification, for example on pages 24-26, and Figs. 3 and 4, and thus, does not contain new matter.

The Examiner contends that the specification does not give any guidance as to the full range of conditions which could be treated or prevented using the instant claimed process. The Examiner further contends that in order to practice the claimed invention, one skilled in the art would have to speculate which conditions could be prevented using the claimed compounds found in the instant claims. Applicants respectfully disagree.

As noted above, the presently amended claims are directed to a method for the treatment of HIV infection. Applicants submit herewith Exhibits A-B as evidence that one having ordinary skill in the art would recognize that the presently claimed compounds could be used for the treatment of HIV infection without undue experimentation.

Exhibit A

The National Institute of Allergy and Infectious Diseases (NIAID) categorizes medications used to treat HIV/AIDS into five major drug classes. One class of HIV/AIDS retroviral drugs as "Fusion/Entry Inhibitors". Fusion/Entry Inhibitors interfere with the virus' ability to fuse with the cellular membrane, thereby blocking entry into the host cell. Applicants submit that the as-filed specification shows data to support that the presently claimed compounds block syncytia formation between HIV infected cells and uninfected CD4 cells (see, for example, Examples 2 and 3 and Figures 3 and 4 of the as-filed specification). The as-filed specification describes this syncytia formation assay as being useful to detect whether compounds have an effect on binding and fusion between the virus and host cell (see page 25, lines 1-3). Moreover, Qin et al., *Helvetica Chimica Acta* – Vol. 89 (2006); pp. 127-133 (copy provided), provide post-filing data that support that the presently claimed compounds block syncytia formation between HIV infected cells and uninfected CD4 cells and could be effective in treating HIV infection (see, Figure 5 and paragraph bridging pages 131 and 132).

Exhibit B

Applicants submit that a structural search of the presently claimed compounds in the NIAID HIV drug database identified Concentricolide (disclosed in the as-filed specification as Concentricolide A) as a compound that can be used to treat HIV/AIDS. Moreover, the data in this chemical database supports that the Qin et al. reference provides valid evidence that Concentricolide A is effective in blocking syncytia formation between HIV infected cells and uninfected CD4 cells.

Applicants respectfully submit that the as-filed specification in combination with the post-filing evidence provides ample guidance with respect to practicing a method for the treatment of HIV infection by administering the presently claimed compounds of claims 1-3.

The as-filed specification also provides substantial guidance regarding the dosage forms, doses, and dosing schedules (see as-filed specification, pages 10-12, for example) for the presently claimed compounds. The specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but determination of the optimum amount in each case can readily be accomplishes by simply routine procedures. *Ex Parte Skuballa,* 12 U.S.P.Q.2d 1570, 1571, 1989 WL 274384 (B.P.A.I. 1989).

The Examiner further contends that there is no established correlation between *in vitro* activity and accompanying treatment of viral infections, especially *in vivo*, and those skilled in the art would not accept allegations in the instant specification, or the *in vitro* data to be reliable predictors of success. In addition, the Examiner contends that there is no proof that the claimed compounds or compositions have ever been administered to a human or to an animal model. Applicants respectfully disagree.

As noted above the NIAID has classified Concentricolide A as a compound in the anti-HIV compound database; thus, one having ordinary skill in the art would appreciate that the *in vitro* data provided in the as-filed specification would be useful for treating HIV infection *in vivo*.

Applicants respectfully submit that the Examiner has not met the initial burden to establish the lack of enablement for the presently claimed invention. Applicants further submit that MPEP states that the initial burden is on the Examiner to give reasons for the lack of enablement. The Examiner must also give reasons for a conclusion of lack of correlation for an

in vitro or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. See MPEP §2164.02.

Applicants respectfully submit that the as-filed specification provides detailed *in vitro* working examples, wherein the presently claimed compounds are shown to have low cytotoxicity (see as-filed specification, Figure 1, for example) and display activity in blocking HIV cell fusion (see as-filed specification, Figure 3, for example) and inhibiting the cytopathic effect of HIV (see as-filed specification, Figure 5, for example). Moreover, the presently claimed compounds displayed comparable results to and fairly correlate to those of AZT and T-20, two well-known HIV therapeutics. Thus, based on results of the presently claimed compounds in the assays exemplified in the as-filed specification, Applicants respectfully submit that one having ordinary skill in the art would be able to practice the presently claimed method without undue experimentation. Moreover, enablement of the claimed invention does not require a demonstration that the invention may be used therapeutically. *In re Brana* 51 F.3d 1560, 1567 (Fed. Cir. 1995). (See also "Legal Analysis Supporting Utility Examination Guidelines 60 F.R. 36263, July 14, 1995.).

Applicants respectfully submit that in view of the as-filed disclosure, one having ordinary skill in the art would not encounter any undue experimentation in practicing the entire breadth of the presently claimed invention. Accordingly, Applicants submit that the as-filed specification fully enables the presently claimed invention. Reconsideration and withdrawal of this basis for rejection is respectfully requested.

CLAIMS REJECTIONS UNDER 35 U.S.C. §112, ENABLEMENT, SECOND REJECTION

Claims 1-6, 9, and 10 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that the as-filed specification does not provide any teaching or guidance for preparing

any specific hydrates or solvates. Applicants respectfully disagree. However, Applicants, without acquiescence and solely in a good-faith effort to expedite prosecution, have amended the claims so that they no longer recite hydrates or solvates. Thus, Applicants respectfully submit that this basis of rejection has been obviated. Reconsideration and withdrawal of this basis for rejection is respectfully requested.

CLAIMS REJECTIONS UNDER 35 U.S.C. §103(A)

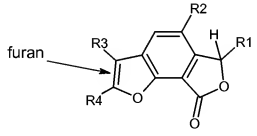
Claims 1-6 and 9 stand rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Padwa *et al.* (DN 138:170018 (2003); "Padwa") and/or Murray *et al.* (DN 106:101992 (1986); "Murray"). Specifically, the Examiner contends that Murray and Padwa teach benzofuranolactone compounds corresponding to those recited in the claims, and that structurally related compounds bearing similar substituents, such as propyl instead of ethyl, would have been obvious to one having ordinary skill in the art as the results would not have been unexpected. The Examiner further contends that claim 6 would have been an obvious method as it is well-known in the art of plant extracts to separate an isolate plant compounds in the manner recited in the claims.

Applicants respectfully traverse this basis for rejection and submit that the Action fails to establish a *prima facie* case of obviousness with respect to the presently claimed subject matter. *See In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) (The USPTO has the burden of showing a *prima facie* case of obviousness). At a minimum, the Examiner must positively demonstrate that the combined references teach or suggest all the claim features, and even assuming, *arguendo,* that the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by Applicants with a reasonable expectation of success. *See KSR v. Teleflex, Inc.,* No 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art").

Applicants respectfully submit that the Examiner is required to provide a clearly articulated rationale to support a prima facie case of obviousness. See MPEP §2141. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the

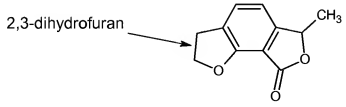
claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396.

Specifically, the Action fails to articulate any clear rationale to modify the furan ring structure of the prior art compounds of Murray and Padwa and arrive at the presently claimed compounds with any reasonable expectation of success. Applicants submit that the presently claimed compounds have a core structure comprising a furan ring. See, for example:



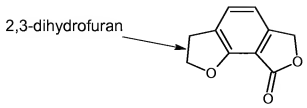
Compounds of Formula I

In contrast, Murray teaches compound RN 106895-67-4, comprising a 2,3-dihydrofuran.



Murray: RN 106895-67-4

Furthermore, Padwa teaches compound RN 289673-95-6, also comprising a 2,3-dihydrofuran.



Padwa: RN 289673-95-6

Applicants respectfully submit that the Examiner has relied on mere conclusory statements and has failed to provide any clearly articulated rationale to support why the prior art would have led the skilled artisan to modify the prior art compounds of Padwa and Murray and arrive at the presently claimed concentricolides with any reasonable expectation of success. Thus, the Action fails to establish a prima facie case of obviousness against the presently claimed invention.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492. F.3d 1350 (Fed. Cir. 2007), the court concluded that in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound. The Takeda Court further noted that "In addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985).

Moreover, MPEP §2144.09 states that "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne,* 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). However, Applicants respectfully submit that neither Murray nor Padwa offer any evidence of a utility for the RN 106895-67-5 or RN 289673-95-6, respectively. Without having defined a utility, there is no motivation for the skilled artisan to modify the compounds of Murray and/or Padwa and arrive at the presently claimed compounds. If the prior art does not teach any specific

or significant utility for the disclosed compounds, then the prior art is **>unlikely< to render structurally similar claims prima facie obvious **>in the absence of any reason< for one of ordinary skill in the art to make the reference compounds **>or< any structurally related compounds. *In re Stemniski*, 444 F.2d 581, 170 USPQ 343 (CCPA 1971). See MPEP §2144.09.

Applicants respectfully submit that the Action has clearly failed to provide a sufficient basis of rationale that would lead the skilled artisan to modify the prior art compounds to arrive at the presently claimed concentricolides. Thus, Action has failed to establish a *prima facie* case of obviousness against the presently claimed compounds.

The Examiner further contends that claim 6 would have been an obvious method as it is allegedly well-known in the art of plants extract to separate and isolate plant compounds in the manner recited in the claims. Applicants respectfully disagree.

Applicants respectfully submit that the Action has failed to provide any evidence, either in the form of prior art references and/or sufficient rationale, that one having skill in the art would be able to carry out an extraction of the fruiting bodies of *Daldinia* as claimed and isolate the presently claimed compounds of Formula II. The Action has merely offered a conclusory statement that the skilled artisan would find the presently claimed method of claim 6 obvious because it was allegedly well-known in the art.

As explained above, the *KSR* Court noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at ___, 82 USPQ2d at 1396.

Applicants respectfully submit that the Action has failed to identify any prior art describing or suggesting a method of making extracts from the fruiting bodies of *Daldinia* that would allow the skilled artisan to predictably isolate the presently claimed compounds of Formula II with any reasonable expectation of success. Thus, the Action has failed to establish a *prima facie* case of obviousness against the presently claimed method of claim 6.

Accordingly, as the Action fails to establish a prima facie case of obviousness against the presently claimed invention, Applicants respectfully request reconsideration and withdrawal of these bases for rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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WTC:jto

Enclosures:
Exhibit A
Exhibit B
Qin et al., *Helvetica Chimica Acta* – Vol. 89 (2006); pp. 127-133

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